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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,383	12/05/2003	Keith Graham Packham	674519-2029	9236

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,383	PACKHAM ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *37-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36 and 41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-43* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-43 are pending in the instant application.

Election/Restrictions

2. Applicant's election of Group I in the reply filed on October 25, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 37-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-36 and 41-43 are currently under examination. Claim 43 is examined as far as it encompasses a method of treatment with a sulphamate compound and apoptosis inducer.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

Claim Objections

4. Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 5 recites "wherein the TRAIL is TRAIL/Apo-2L", and TRAIL and Apo-2L are the same cytokine. Should Applicants traverse the objection, Applicants should explain the difference in scope between TRAIL and Apo-2L.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-3 and 8-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,676,934. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-14 of U.S. Patent No. 6,676,934 are drawn to a composition comprising a polycyclic sulphamate compound and TNF-α (apoptosis inducer), and claims 1-3 and 8-32 of the instant application are drawn to a composition comprising a sulphamate compound which may

be polycyclic and an apoptosis inducer, and wherein the composition further comprises a pharmaceutically acceptable carrier, diluent or excipient. It would have been prima facie obvious for one of skill in the art to add a pharmaceutically acceptable carrier, diluent or excipient in order to make a pharmaceutically acceptable composition that could be used to test for activity in an animal model.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 Claims 1-36 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification teaches that oestrone-3-suphamate (EMATE), 2-meothxy oestrone-3-O-sulphamate (2-MeO EMATE), 2 ethyloestrone-3-O-sulphamate (2-EtEMATE), and 2-meothxyoestrone-3-O,17-bissulphamate (2-MeO2bis EMATE), analogues of each other, are highly potent in preventing and/or inhibiting growth of breast cancer cells, and the specification also teaches the cytokine TRAIL, which is an apoptosis inducer. However, the specification does not disclose all sulphamates and apoptosis inducers that are highly potent in preventing or inhibiting growth of breast cancer cells alone or in combination. The claims as written, however, encompass all sulphamates and apoptosis inducers which were not originally contemplated and fail to meet the written description provision of 35

USC 112, first paragraph, because the written description is not commensurate in scope with the recitation of claims 1-36 and 41-43. The specification does not provide written description for all sulphamates. *Vas-Cath Inc. v Mahurkar,* 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize [he or she] invented what is claimed. (See *Vas-Cath* at page 1116.) Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

With the exception of the highly analagous compounds EMATE, 2-MeO EMATE, 2 EtEMATE, and 2-MeO2bis EMATE, the skilled artisan cannot envision the detailed structure of the claimed sulphamate compounds and the apoptosis inducers, regardless of the complexity or simplicity of the method of identifying the compounds. As a result, it does not appear that the inventors were in possession of the invention to use all sulphamates or apoptosis inducers set forth in the claims.

6.2 Claims 1-36 and 41-43 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a steroidal sulphamate compound and TRAIL, does not reasonably provide enablement for a composition comprising a non-steroidal sulphamate compound and any apoptosis inducer, a non-steroidal sulphamate compound and TRAIL, or a steroidal sulphamate compound and any apoptosis inducer. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the invention commensurate in scope with these claims. The instant specification discloses a number of experiments in which it is demonstrated that the analogous compounds EMATE, 2-MeO EMATE, 2 EtEMATE, and/or 2-MeO2bis EMATE, caused apoptosis of breast cancer cells in vitro, and activated caspases 3 and 8. Co-treatment with TRAIL increased apoptosis of the cells, and co-treatment with TRAIL also enhanced activation of capsase 3. The effects of co-administration with the oestrone compounds and TRAIL appear to be synergistic. However, claims 1-36 and 41-43 encompass compositions comprising either a non-steroidal sulphamate compound and any apoptosis inducer, a non-steroidal sulphamate compound and TRAIL, or a steroidal sulphamate compound and any apoptosis inducer.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988). As stated in the MPEP, 2164.01(a), "The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407." "The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination.

Rather, it is a conclusion reached by weighing all the above noted factual considerations. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404."

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification that compositions comprising any sulphamate compound and apoptosis inducer would have the same activities as that of EMATE, 2-MeO EMATE, 2 EtEMATE or 2-MeO2bis EMATE and TRAIL. It is not predictable that any sulphamate compound and any apoptosis inducer would have the same activities. Thus, the specification fails to teach the skilled artisan how to use the compositions without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to use the invention commensurate in scope with the claims.

6.3 Claims 32-36 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventing or inhibiting growth of tumor cells or inducing apoptosis of a cell or activating a caspase, comprising contacting cells in vitro with EMATE, 2-MeO EMATE, 2 EtEMATE or 2-MeO2bis EMATE, and TRAIL, does not reasonably provide enablement for a method of treatment of a subject with EMATE, 2-MeO EMATE, 2 EtEMATE or 2-MeO2bis EMATE and TRAIL. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. As discussed above, the specification is enabling for methods of inhibiting growth of tumor cells or inducing apoptosis of a cell or activating a caspase in vitro, comprising contacting cells in vitro with a EMATE, 2-MeO EMATE, 2 EtEMATE or 2-MeO2bis EMATE, and TRAIL.

T. Gura, Science, Vol. 278, Nov. 1997, pages 1041-1042, teaches that it is not predictable that potential anticancer drugs that screen positively in human cells in culture would be effective when administered to a subject, partly because cell culture provides no information about whether a drug will make it to the tumor sites (page 1041, first column, 3rd paragraph). Rakesh Jain, Science, Feb. 23, 1996, Vol. 271, and Rakesh Jian, Cancer and Metastasis Revies, 1990, Vol. 9, pages 253-266, also teaches that delivery of anticancer agents to solid tumors in effective quantities with minimal toxicity is a major problem. Gerald Dermer, Bio/Technology, March 1994, Vol. 12, page 320, teaches that human cancer cells in vitro are poor representatives of malignancy in vivo, with characteristics profoundly different from the human disease, and that the widely disparate character of human tumor cell lines contributes greatly to chemotherapy's continued ineffectiveness against cancer. Therefore, the art teaches that even if an anticancer treatment is effective using malignant cell lines in vivo, it is more likely than not that the treatment would be ineffective in a subject. Even anticancer treatments that are effective in mouse models are not predictive of treatment of humans. Treatments that appeared effective in xenograph models of human tumor cells in mice worked poorly in humans, since xenograph tumors don't behave like naturally occurring tumors in humans (T. Gura, Science, Vol. 278, Nov. 1997, pages 1041-1042).

Therefore, due to the lack of working examples in the specification, and the prior art which teaches that an antitumor agent that is effective in cell culture in vitro is more likely than not to be effective in a human subject, it is not predictable that a composition comprising EMATE, 2-MeO EMATE, 2 EtEMATE or 2-MeO2bis EMATE, and TRAIL would prevent or inhibit growth of tumor cells in a subject.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-7 are indefinite because claims 4 and 6 encompass an apoptosis inducer that is "a tumour necrosis factor apoptosis inducing ligand" and the TRAIL in parentheses, and it is not clear if what is being claimed is tumour necrosis factor or TRAIL, which are two different cytokines and bind to different receptors.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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Patent Examiner

Eileen B. O'Hara

EILEEN B. O'HARA
PATENT EXAMINER